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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/648,593	08/26/2003	Fei Huang	D0273 NP	5265

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EXAMINER	
SWOPE, SHERIDAN	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 03/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/648,593	HUANG ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-52* is/are pending in the application.

4a) Of the above claim(s) *42-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41 and 52* is/are rejected.

7)☒ Claim(s) *52* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 August 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0804; 0205*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election, without traverse, of Invention I, Claims 41 and 52, in their response of December 21, 2005 is acknowledged. Claims 41-52 are pending. Claims 42-51 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 41 and 52 are hereby examined.

Priority

The priority date of the instant invention is taken to be August 27, 2002, the filing date of provisional application US60/406,385.

Title

It is suggested the title be amended to reflect the instant invention, which is using the gene for EphA2 as a predictor for responsiveness of cancer cells to a kinase inhibitor.

Specification-Abstract

The abstract is objected to for being too long.

MPEP 608.01(b) states

> The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

Drawings

Figures 1 and 7 are objected to because the Office's copies are illegible.

Figure 2 is objected to for being confusing. The A panel of said figure does not have the same number of control and BMS-A treated samples; likewise, the B panel of said figure does

not have the same number of control and BMS-A treated samples. The Examiner questions whether the vertical line separating panels A and B should be moved to the right.

Claims-Objections

Claim 52 is objected to for reciting non-elected subject matter and being dependent upon non-elected claims.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Double Patenting

> The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
> A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).
> Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Claims 41 and 52 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 16 of US Application 11/072,175. Although

the conflicting claims are not identical, they are not patentably distinct from each other. Claims 41 and 52 herein and Claim 16 of 11/072,175 are both directed to methods for determining the effect of a compound on the expression of gene products. Specifically, they are directed to determining the effect of BMS-A on the expression of gene products from the Hs.171596 (EphA2) gene. The claims differ in that Claim 16 of 11/072,175 also recites methods for determining the effect of additional compounds on the expression of additional gene products. The portion of the specification in 11/072,175 (Table 2; Fig 4) that supports the recited methods includes embodiments that would anticipate Claims 41 and 52 herein, e.g., methods for determining the effect of BMS-A on the expression of gene products from the Hs.171596 (EphA2) gene. Claims 41 and 52 herein cannot be considered patentably distinct over Claim 16 of 11/072,175 when there are specifically recited embodiments, methods for determining the effect of BMS-A on the expression of gene products from the Hs.171596 (EphA2) gene, that would anticipate Claims 41 and 52 herein. Alternatively, Claims 41 and 52 herein cannot be considered patentably distinct over Claim 16 of 11/072,175 when there are specifically disclosed embodiments in 11/072,175 that supports Claim 16 of that application and falls within the scope of Claims 41 and 52 herein, because it would have been obvious to a skilled artisan to modify the methods of Claim 16 of 11/072,175 by selecting a specifically disclosed embodiment that supports those claims, i.e., methods for determining the effect of BMS-A on the expression of gene products from the Hs.171596 (EphA2) gene, as disclosed in 11/072,175. One having ordinary skill in the art would have been motivated to do this, because such an embodiment is disclosed as being a preferred embodiment within Claim 16 of 11/072,175.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 41 and 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons.

Claim 41 recites the gene for EphA2 by a database accession number, Hs.171596, which is accessed by the internet. USPTO policy does not permit the USPTO, i.e, via an issued patent, to link to any commercial sites, since the USPTO exercises no control over the organization, views, or accuracy of the information contained on these outside sites and the content within is likely to change over time. In addition, the sequence found at said site, set forth by GenBank Accession Number NM_004431 as disclosed in Table 2, is not identical to SEQ ID NO: 1 herein (see enclosed alignment). Claim 53, as dependent from Claim 41, is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the same reason.

Claim 41 recites the limitation "said sample" in lines 5 and 6. There is insufficient antecedent basis for this limitation in the claim. Claim 53, as dependent from Claim 41, is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the same reason.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 42 and 52 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for methods of identifying breast cancer cells that are sensitive to BMS-A or any tyrosine kinase inhibitor by determining the effect of any said tyrosine kinase inhibitor on the expression of any EphA2 gene product in any breast cancer cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In regards to this enablement rejection, the application disclosure and claims are compared per the factors indicated in the decision In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of a comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claim 42 is so broad as to encompass a method of identifying breast cancer cells that are resistant or sensitive to treatment with any protein tyrosine kinase inhibitor by determining the effect of any said protein tyrosine kinase inhibitor on the expression of an EphA2 gene product

in any said breast cancer cells. Claim 52 is so broad as to encompass a method of identifying breast cancer cells that are resistant or sensitive to treatment with the BMS-A protein tyrosine kinase inhibitor by determining the effect of BMS-A on the expression of an EphA2 gene product in any said breast cancer cells. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the large number of protein tyrosine kinase inhibitors and large number of breast cancer cells broadly encompassed by the claim.

The specific reagents and steps used for identifying any breast cancer cell that can be successfully treated with any protein tyrosine kinase inhibitor determine the method's success. Predictability of which steps and reagents can be used to obtain the desired effect requires a knowledge of how said steps and reagents relate to the desired outcome. Specifically, predictability of which of the large number of breast cancer cells can be contacted with any one of a large number protein tyrosine kinase inhibitors in order to determine which breast cancer cells can be successfully treated with any one of said inhibitors requires guidance with regard to which each breast cancer cells have a protein tyrosine kinase that is inhibited by any specific inhibitor, whether inhibition of said tyrosine kinase regulates the expression of an EphA2 gene product, and whether inhibition of said EphA2 gene product would have the desired effect of treating the breast cancer cell. However, in this case the disclosure is limited to a method of using "BMS-A" kinase inhibitor for correlating regulation of an EphA2 gene expression product with treatment of breast cancer cells; however, the structure of the "BMS-A" kinase inhibitor not disclosed by the specification or the art.

Methods for testing the effects of any compound on the activity of any protein tyrosine kinase as well as methods for testing the effect of any compound on expression of an EphA2 gene product and on the ability to inhibit the growth of breast cancer cells are known in the art. However, it is not routine in the art to screen an essentially unlimited number of compounds as protein tyrosine kinase inhibitors or to screen a very large number of compounds that are known protein tyrosine kinase inhibitors for an effect on EphA2 gene expression and on the growth of a large number of breast cancer cells. Furthermore, the steps and reagents to be used with a reasonable expectation of success in obtaining the desired treatment of identifying breast cancer cells that can be successfully treated are limited and unpredictable (Fernandez-Trigo et al, 1995; Woll, et al 1999). In addition, one skilled in the art would expect any tolerance to modification of any successful method for identifying breast cancer cells that can be successfully treated with a protein tyrosine kinase inhibitor to diminish with each further and additional modification of steps and reagents used.

The specification does not support the broad scope of Claim 42 which, encompasses all methods of identifying breast cancer cells that are resistant or sensitive to treatment with any protein tyrosine kinase inhibitor by determining the effect of any said protein tyrosine kinase inhibitor on the expression of an EphA2 gene product in any said breast cancer cells. The specification also does not support the broad scope of Claim 53, which encompasses all methods of identifying breast cancer cells that are resistant or sensitive to treatment with the BMS-A protein tyrosine kinase inhibitor by determining the effect of BMS-A on the expression of an EphA2 gene product in any said breast cancer cells. The specification does not support the broad scope of Claims 42 and 52 because the specification does not establish:

(A) the structure of any protein tyrosine kinase inhibitor, including BMS-A, that can be used to identify breast cancer cells that can be successfully treated with the inhibitor by determining the effect of the inhibitor on the expression of an EphA2 gene product; (B) regions of the inhibitor structure which may be modified without effecting the kinase inhibition and treatment of breast cancer cells; (C) the general tolerance of the kinase inhibition and treatment of breast cancer cells to modification of the inhibitor structure and extent of such tolerance; (D) a rational and predictable scheme for modifying any protein tyrosine inhibitor with an expectation of obtaining the desired biological function; (E) the types of breast cancer cells that comprise any specific protein tyrosine kinase that is inhibited by any specific kinase inhibitor and whether inhibition of said kinase inhibits growth of the breast cancer cell; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices compounds are protein tyrosine kinase inhibitors and which breast cancer cells would be successfully inhibited by said kinase inhibitors.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method for identifying any number of breast cancer cells that are sensitive to "BMS-A" or any tyrosine kinase inhibitor by determining the effect of any said tyrosine kinase inhibitor on the expression of any EphA2 gene product in any said breast cancer cell. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the

experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Written Descripition

Claims 41 and 52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of methods for identifying any number of breast cancer cells that are sensitive to "BMS-A" or any tyrosine kinase inhibitor by determining the effect of any said tyrosine kinase inhibitor on the expression of any EphA2 gene product in any said breast cancer cell. The specification teaches no representative species of such methods. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being a method for identifying any number of breast cancer cells that are sensitive to "BMS-A" or any tyrosine kinase inhibitor by determining the effect of any said tyrosine kinase inhibitor on the expression of any EphA2 gene product in any said breast cancer cell. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Examiner's note: It is acknowledged that the specification states: "The protein tyrosine kinase inhibitor compound, BMS-A, utilized for identifying the polynucleotide predictor sets of this invention, was described in WO 00/62778, published Oct. 26, 2000". However, searching a

PDF version of WO 00/62778 for the terms "BMS-A" and "BMS" failed to reveal to the Examiner any information on a compound named "BMS-A".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kassenbrock et al, 2002 in view of Wang et al, 2002 and further in view of Ogawa et al, 2000. Kassenbrock et al teach that, in a human breast cancer cell line, the Src-class tyrosine kinase inhibitor PP1 inhibits Cbl phosphorylation (Fig 6) and EGF-R ubiquitination (Fig 8) leading to the proposal that phosphorylation of Cbl by a Src-class kinase leads to ubiquitination and down-regulation of the EGF-R (pg 24974; parg 8). Kassenbrock et al do not teach that PP1 regulates the expression level of EphA2. Wang et al teach that Cbl down-regulates EphA2 (Fig 2). Based on said teachings, a person of ordinary skill in the art would believe that, more likely than not, PP1 by inhibiting Cbl phosphorylation would also down-regulate EphA2. Ogawa et al teach that EphA2 is highly expressed in breast cancer cells and that inhibition of EphA2 function inhibits tumor neovascularization (Fig 1; Table 1; Abstract). Thus, based on the combined teachings of Kassenbrock et al, Wang et al, and Ogawa et al, the skilled artisan would believe that, more likely than not, down-regulation of EphA2 by PP1 would inhibit tumor growth and survival by inhibiting tumor neovascularization (see specifically Ogawa et al, pg 6044, parg 1). It would have been obvious to a person of ordinary skill in the art to use the method of Kassenbrock et al

to test the effect of PP1 on EphA2 expression levels in breast cancer cells and to conclude that, if EphA2 was down-regulated by PP1, the cancer cells would be sensitive to treatment with PP1. Motivation to use said methods derives from the desire to determine if PP1 would be successful for treatment of a patient with breast cancer. The expectation of success is high, as high levels of EphA2 are predictive of tumor growth and the art teaches that, more likely than not, PP1, via inhibition of Cbl phosphorylation, would down-regulate EphA2. Therefore, Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kassenbrock et al, 2002 in view of Wang et al, 2002 and further in view of Ogawa et al, 2000.

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages. It is also requested that Applicants identify support, within the original application, for any amendments to the claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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PRIMARY EXAMINER